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10/786,457	02/26/2004	Xudong Yao	108172-00107	9059

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ARENT FOX PLLC
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER	
KHANNA, HEMANT	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,457	YAO ET AL.	
	Examiner	Art Unit	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4-6 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of claims 1-15 that belong to Group I in the reply filed on November 03, 2006 is acknowledged.

Applicant's election of species, namely trypsin in the reply filed on November 3, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the election of species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The elected species is embraced by claims 1-3, and 7-15. Applicant's species has not been found free of the prior art.

Claims 1-3, 7-15 are currently pending.

Claims 4-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. **Claims 16-20** are withdrawn from further consideration as being drawn to a non-elected invention. Election was made **without** traverse in the reply filed on November 03, 2006.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-3, 7-15 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The method of claim 1 is directed to a method of labeling peptides comprising the steps of obtaining peptides formed from proteins digested by trypsin and incorporating isotopic atoms into peptides in the catalytic presence of trypsin. Claims 2, 3, 7-15 further comprise the step of incorporating isotopic atoms from $H_2{}^{18}O$, and analyzing the peptides by mass spectrometry. The specification on p. 1 discloses that stable isotope labels facilitate proteomic studies. However the disclosed utility is not applicable to the instant claims. For example, the result of the method of claims 1-3, 7-15 is an analysis of the extent of isotope incorporation to study the enzyme-catalyzed exchange of oxygen. A method of labeling proteins MAY have "substantial" utility if one knew the purpose of labeling proteins, and/or the parameters of analyzing biological changes in diseased tissues by MS, or the purpose of the relative quantitation of poorly abundant proteins. However, the specification does not disclose any specific utility for the invention because the claims do not recite a protein target, protein copy number, tissue, disease, and phenotype being analyzed with the purpose of carrying out proteomic studies. In the order for the result of the method to be used for proteomics, one skilled in the art must be aware of the correlation between the isotope information received, and say, the relative quantitation of expression levels of proteins from proteome pools to be compared. Absent any disclosure of proteins, their importance, a goal of labeling peptides, a goal of MS and a correlation between the information received from such studies with proteomic parameters, the asserted utility is not specific. No such information is recited in the claims. Applicant is reminded that a "use" to perform

research is not a utility under 35 U.S.C. 101. For the reasons set forth above, the invention lacks a specific utility, and therefore lacks a patentable utility.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 7-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites in the preamble "a method of labeling peptides". None of the steps is actually directed to labeling peptides. It is not clear whether the method comprises an additional labeling step, since the result of "incorporating isotopic atoms" encompasses those isotopes, which are not labels, such as ^{16}O. The incorporation of an isotope atom such as ^{16}O would not result in a mass shift for the carboxyl terminating proteolytic fragment, thereby preventing the fragment from being recognized in a protein digest pool. It is not clear if the preamble is intended to limit the method and what relationship is intended between the preamble and the method steps. Thus claim 1 is indefinite. Claims 2-3, 7-15 depend from claim 1, and therefore are indefinite.

Claim 1 recites the limitation "catalytic presence of proteolytic enzymes". It is not clear whether this limitation is intended to limit the claim as the result of the enzyme presence is no different than from its catalytic presence, since proteolytic enzymes are used in catalytic quantities. Thus claim 1 is indefinite.

Claim 10 recites the limitation "peptides that have not been labeled". It is not clear what is intended to be limited by the above-mentioned limitation whether the labeling reaction of peptides was not quantitative or did the reaction use a non-label isotope, such as ^{16}O.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for methods to incorporate isotopic ^{18}O in the presence of trypsin, does not reasonably provide enablement for the methods to incorporate other isotopic atoms proteolytically such as ^{15}N or ^{14}C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claim 1.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Nature of the invention. The instant invention is to methods for labeling proteolytic fragments by incorporation of ^{18}O as the isotope atom in the presence of trypsin and to analyze a mixture of labeled and unlabeled peptides using MS.

Breadth of the claims. According to the language of the claims, the method for incorporating isotope atoms into proteolytic fragments can be extrapolated to any isotopic atom in the catalytic presence of trypsin.

State and un/predictability of the prior art. The claimed subject matter is lacking in predictability. No example exists for the incorporation of isotope atoms other than ^{18}O using trypsin into proteolytic fragments. Specifically, Schnolzer teaches the "observed incorporation of a second atom of ^{18}O into the K or R carboxyl group indicates that the tryptic fragment is accepted as a pseudo-substrate to form a covalent ester intermediate which is hydrolyzed again in a futile cycle (Results and discussion, page 946-947;

Figure 2, page 947). The reversibility of the hydrolysis step leads to complete equilibration of solvent oxygen at both K and R carboxyl oxygens of the proteolytic fragments". At the time the invention was made, the successful incorporation of all isotope atoms by trypsin into proteolytic fragments was not routinely obtainable by those skilled in the art. It is presumed that the Applicant's intent is to incorporate ^{18}O, in the catalytic presence of trypsin into a proteolytic fragment. Since the success in the incorporation of ^{18}O depends on repeated binding/hydrolysis cycles in presence of only $H_2{}^{18}O$, the incorporation of all other isotope atoms, is not enabled.

Working examples. Although examples are disclosed in the specification that demonstrate the incorporation of ^{18}O by trypsin into proteolytic fragments via the use of $H_2{}^{18}O$ no examples are provided that would suggest the incorporation of other isotopic atoms into proteolytic fragments in the presence or absence of $H_2{}^{18}O$.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods to extrapolate means of administration of all isotope atoms into proteolytic fragments using trypsin as the proteolytic enzyme. There is a lack of predictability in the art regarding the incorporation of other isotope atoms into proteolytic fragments using trypsin as the proteolytic enzyme.

Amount of experimentation necessary. Given the unpredictability of the art in view of the incorporation of other isotope atoms into proteolytic fragments, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate with the scope of the claim. Although the applicants have identified an interesting ^{18}O labeling

method that uses proteolytic enzymes, but essentially all of the work required to label peptides with any isotopic atom, needs to be further undertaken.

Relative Skill of those skilled in the art. In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a Ph.D. with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is Ph.D. predictability of the results is not invariable.

In consideration of each of the factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer et al (Electrophoresis (1996) 17:945-953) in view of Yao (Anal. Chem. (2001) 73: 2836-2842).

The instant claims recite a method of labeling peptides comprising the steps of obtaining proteolytic fragments and incorporating ^{18}O in the presence of trypsin.

Further, the instant claims recite the analysis of a mixture of labeled and unlabeled peptides by mass spectrometry.

With respect to claims 1-3, 7-9 Schnolzer disclose digesting proteins with proteases in enriched $H_2{}^{18}O$ using trypsin as a protease. Schnolzer also teach that the digestion by the protease resulted in a mass shift of +4D, that resulted from the proteolytic fragment obtained from the initial cleavage reaction undergoing repeated binding/hydrolysis cycles, resulting in the complete equilibration of both oxygens in the carboxy terminus of the fragments with oxygen from $H_2{}^{18}O$ (abstract). Further, Schnolzer exemplify their conclusions by studies of peptide fragments with "K" or "R" as C-terminus whose carboxyl function incorporates a second molecule of $H_2{}^{18}O$ indicating that the tryptic fragment with "K" or "R" as the C-terminus is accepted as a pseudo-substrate, which undergoes repeated binding and hydrolysis (Results and discussion, page 946-947; Figure 2).

With respect to claim 1, while Schnolzer differs from the instant claims by teaching that both the proteolytic cleavage and catalytic labeling occur in presence of $H_2{}^{18}O$, it would be obvious to one of ordinary skill in the art at the time of the invention to introduce $H_2{}^{18}O$ as the ^{18}O donor in the catalytic labeling step only so as to provide a means for the known and expected result of complete equilibration of both oxygens resulting in a mass shift of +4D to enable accurate protein sequencing of the C-terminus by MS.

With respect to claims 10-15, Schnolzer discloses as described above, and further discloses that it is known in the art that both trypsin and Lys-C are interchangeable in their ability to incorporate two atoms of ^{18}O for the peptide fragments. In view of Yao the combination of the proteolytic fragments obtained from the trypsin mediated hydrolysis of an adenovirus protein in $H_2{}^{18}O$ with the proteolytic fragments obtained from the trypsin mediated hydrolysis in $H_2{}^{16}O$ is taught. The combination was then analyzed on an ion cyclotron resonance mass spectrometer for the isotopic peak distribution in the two sets of fragments, each fragment with a set of peaks separated from those of higher masses by +4D (left column, page 2839). Yao teaches the calculation of the theoretical isotope peak distribution with formula (II) in the instant claim 12 (left column, page 2839) for the incorporation of one ^{18}O or two ^{18}O isotopic atoms.

With respect to claims 10-15, Yao differs from the instant claims by obtaining the proteolytic fragments from a combination treatment involving both Lys-C and trypsin.

In view of the above teachings it would be obvious to one of ordinary skill in the art at the time of the invention to remedy the deficiency of Schnolzer with the mixing of proteolytic fragments that are labeled and unlabeled in presence of trypsin for the known and expected result of providing a means recognized in the art for simplifying the deduction of sequences from differential isotope labels.

With respect to claims 14 and 15, in view of the teachings of Schnolzer and Yao it would be obvious to one or ordinary skill at the time of the invention to optimize the percent labeling and proteolytic incubation times because such variables are art

recognized variables that are routinely optimized to provide an effective means for the known and expected result of complete equilibration of both carboxyl oxygens.

Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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Hemant Khanna Ph.D.
December 01, 2006

B. DELL CHISM
PRIMARY EXAMINER